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(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF WASHINGTON** [US/US]; Office of Technology Licensing, 1107 NE 45th Street, Suite 200, Seattle, WA 98105-4631 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **REH, Thomas, A.** [US/US]; 9006- 25th Avenue NE, Seattle, WA 98115 (US). **SEIBEL, Eric, J.** [US/US]; 4114 Wallingford Avenue N, Seattle, WA 98103 (US).

(74) Agent: **MCGURL, Barry, F.**; Christensen O'Connor Johnson Kindness PLLC, 1420 Fifth Avenue, Suite 2800, Seattle, WA 98101 (US).

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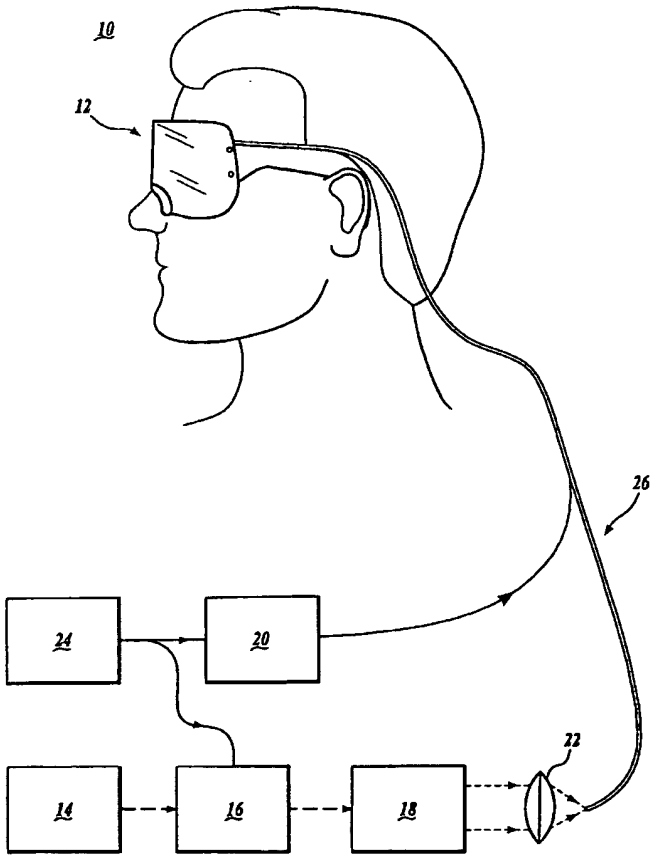
(54) Title: METHODS FOR MODULATING NEURAL ACTIVITY IN THE RETINA



(57) Abstract: In one aspect, the present invention provides methods for modulating neural activity in the retina of a mammalian eye, wherein the methods each comprise the step of irradiating the retina of a mammalian eye with light energy (14,16,18,22,26), wherein: (a) the retina comprises a photoactivatable precursor molecule comprising a neuroactive molecule linked to a photoabsorbent molecule; and (b) the light energy releases the neuroactive molecule from the photoabsorbent molecule, the released neuroactive molecule interacting with one or more retinal neurons thereby modulating neural activity in the retina.

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METHODS FOR MODULATING NEURAL ACTIVITY IN THE RETINA

FIELD OF THE INVENTION

The present invention relates to methods for modulating neural activity in a mammalian retina, and to methods for producing artificially formed vision in a mammalian eye.

BACKGROUND OF THE INVENTION

The mammalian eye includes a cornea, a fluid-filled anterior chamber, a lens, a fluid-filled posterior chamber, and a photosensitive retina. The designations "anterior" and "posterior" are with reference to the lens. Light enters the eye through the cornea, passes through the anterior chamber and is focussed onto the retina by the lens. The retina is composed of numerous types of cells including photosensitive rods, which are responsible for night vision, and photosensitive cones that are responsible for high acuity day vision. The rods and cones communicate with neurons in the retina which transmit nerve impulses to the visual centers of the brain where this information is processed to generate the perception of visual information. For example, rods and cones communicate with bipolar cells, which, in turn, communicate with ganglion cells that transmit nerve impulses to the brain.

Many people become blind through the degeneration of the rods and/or cones in the retina. This type of blindness has many causes, some of which are the results of known, underlying, genetic mutations, while others are of unknown cause. In the condition known as retinitis pigmentosa, the rods degenerate first, and the individuals lose their night vision, and later the cones degenerate, resulting in total blindness. In the condition known as age-related macular degeneration, or AMD, the cones degenerate, and since they are necessary for high acuity vision, these individuals also become functionally blind. In both diseases the non-photoreceptive neurons, such as the bipolar and ganglion cells, remain largely intact.

There are currently no treatments for most diseases that cause the degeneration of photoreceptors. There have been attempts, however, to develop a retinal prosthesis by the implantation of multiple active electrodes which sense light impinging on the retina and generate corresponding electrical signals that stimulate the healthy bipolar and/or

ganglion cells (*see, e.g.*, Dagnelie, G. and R.W. Massof, *IEEE Spectrum,* May, 22-29 (1996); Liu, W., et al., *IEEE Journal of Solid-State Circuits*, **35(10)**:1487-1497 (2000); Chase, V.D., *Technology Review*, May/June, **102**:44-48, (1999); and Haystead, J., *Vision Systems Design*, **4(6)**:31-36 (1999)). Implanted electrode arrays have significant limitations, however, such as power dissipation, incompatibility with surrounding biological tissues, and the lack of knowledge about the neural interconnections to the bipolar and ganglion cells, and the type of stimulation required to mimic retinal signal processing.

Thus, there is a continuing need for methods and devices for stimulating, inhibiting, or otherwise modulating, the activity of retinal neurons, in diseased retinas in which the photosensitive cells are functionally impaired, in order to generate a pattern of nerve impulses that are transmitted to the visual centers of the brain to yield visual information.

SUMMARY OF THE INVENTION

In accordance with the foregoing, the present invention provides methods for modulating neural activity in the retina of a mammalian eye. In the practice of the methods of the invention, a retina, that includes photoactivatable precursor molecules that each include a neuroactive molecule linked to a photoabsorbent molecule, is irradiated with an amount of light energy that is effective to release the neuroactive molecule from the photoabsorbent molecule. The released neuroactive molecule interacts with one or more neurons in the retina, thereby modulating neural activity in the retina (*e.g.*, stimulates or inhibits the production of nerve impulses in one or more types of neurons in the retina). The modulated neural activity in the retina provides visual information to the brain. The released neuroactive molecule(s) may be molecules that are normally released by rods and/or cones, and that interact with retinal neurons to modulate neural activity and thereby provide visual information to the brain.

Thus, in one aspect, the present invention provides methods for modulating neural activity in the retina of a mammalian eye, wherein the methods each comprise the step of irradiating the retina of a mammalian eye with light energy, wherein: (a) the retina comprises a photoactivatable precursor molecule comprising a neuroactive molecule linked to a photoabsorbent molecule; and (b) the light energy releases the neuroactive molecule from the photoabsorbent molecule, the released neuroactive molecule

interacting with one or more retinal neurons thereby modulating neural activity in the retina. Typically the retina comprises a multiplicity of photoactivatable precursor molecules. Optionally, the methods of this aspect of the invention include the step of providing the photoactivatable precursor molecule(s) to the retina before irradiating the retina with light energy.

The methods of the invention are useful in any situation in which modulation of neural activity in the retina of a mammalian eye is desired. For example, the methods of the invention can be used to stimulate, inhibit, or otherwise modulate, neural activity in the retina of a diseased mammalian eye in which the rods and/or cones are functionally impaired, thereby providing the brain with useful visual information. In particular, the methods of the invention can be used to stimulate, inhibit, or otherwise modulate, neural activity in the retina of a mammalian eye that is suffering from macular degeneration or retinitis pigmentosa. In some embodiments, the present invention is useful for forming artificially formed vision in the retina of a mammalian eye. Again by way of example, the methods of the invention can be used to enhance the vision of a mammal in which the function of the retinal rods and/or cones is impaired, but in which the retinal neurons (*e.g.*, bipolar cells and ganglion cells) are substantially or completely intact.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

The FIGURE shows a representative embodiment of a system for practicing a method of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In one aspect, the present invention provides methods for modulating neural activity in the retina of a mammalian eye (such as a human eye). The methods of this aspect of the invention comprise the step of irradiating the retina of a mammalian eye with light energy, wherein: (a) the retina comprises a photoactivatable precursor molecule comprising a neuroactive molecule linked to a photoabsorbent molecule; and (b) the light energy releases the neuroactive molecule from the photoabsorbent molecule, the released

neuroactive molecule interacting with one or more retinal neurons thereby modulating neural activity in the retina. Typically the retina comprises a multiplicity of photoactivatable precursor molecules.

The term "modulating neural activity in the retina of a mammalian eye" encompasses any change in the frequency and/or pattern of nerve impulses in any type of neuron (*e.g.*, bipolar cells and ganglion cells) in the retina of a mammalian eye. For example, the frequency of nerve impulses in one or more types of neurons in the retina of a mammalian eye can be increased or decreased by treating the retinal neurons in accordance with the methods of the present invention.

The term "light energy" includes infrared, visible and ultraviolet light energy.

Examples of neurons that are located in the retina of a mammalian eye include, but are not limited to, bipolar cells (including ON and OFF subtypes, and rod and cone subtypes), ganglion cells (including ON and OFF subtypes, bistratified subtype, red/green color opponent subtype, and blue/yellow color opponent subtype), horizontal cells and amacrine cells (which include numerous subtypes).

In the practice of the invention, a photoactivatable precursor molecule, which includes a neuroactive molecule linked to a photoabsorbent molecule, is present in, and/or on, the retina of a mammalian eye. Representative examples of useful neuroactive molecules include Ca^{2+} ions, glutamate, glycine, γ-aminobutyric acid (GABA), acetylcholine, dopamine, substance-P, and γ-guanosine triphosphate (γ-GTP).

Useful photoabsorbent molecules interfere with the biological activity of the neuroactive molecule, rendering the neuroactive molecule completely, or substantially, unable to modulate neural activity in the retina of a mammalian eye. Photoabsorbent molecules useful in the practice of the invention absorb light energy which causes the photoabsorbent molecule to release the neuroactive molecule to which it is linked. An exemplary mechanism whereby a neuroactive molecule is released from the photoabsorbent molecule to which it is linked is cleavage of the chemical bond(s) that links the neuroactive molecule to the photoabsorbent molecule. Again by way of example, some photoactivatable precursor molecules include a neuroactive molecule that is non-covalently linked (*e.g.*, by hydrogen bonds, and/or ionic interactions) to a photoabsorbent molecule (*e.g.*, a calcium ion can be non-covalently bound by a photoabsorbent calcium-binding protein); the photoabsorbent molecule absorbs light

energy and changes its physical conformation, thereby releasing the bound neuroactive molecule.

Representative examples of photoabsorbent molecules include derivatives of *o*-nitrobenzylic compounds. The nitrobenzyl group can be synthetically incorporated into the neuroactive molecule, for example, by linkage to a heteroatom (usually oxygen, sulfur or nitrogen) as an ether, thioether, ester (including phosphate or thiophosphate esters), amine or similar functional group. Representative examples of useful nitrobenzyl groups include carboxy-2-nitrobenzyl, 4,5-dimethoxy-2-nitrobenzyl, and 5-carboxymethoxy-2-nitrobenzyl. A nitrobenzyl group can be cleaved from the neuroactive molecule to which it is linked by irradiation with light energy having a wavelength of less than 360 nm. Other representative photoabsorbent molecules include trans-*o*-cinnamoyl and *m*-nitrophenyl groups.

One or more photoabsorbent molecules can be covalently attached to a neuroactive molecule by any art-recognized means (*see, e.g.*, Gee K.R., et al., "Synthesis, Photochemistry, and Biological Characterization of Photolabile Protecting Groups for Carboxylic Acids and Neurotransmitters," *Methods Enzymology* **291**:30-50 (1998); *Methods in Enzymology*, Vol. 291 "Caged Compounds", Gerard Marriott, ed., Academic Press (1998), both of which publications are incorporated herein by reference).

Representative examples of photoactivatable precursor molecules include *N*-(α-carboxy-2-nitrobenzyl) carbamylcholine; γ-aminobutyric acid, α-carboxy-2-nitrobenzyl ester; *N*-methyl-D-aspartic acid, β-(2,2'-dinitrobenzhydryl) ester; *N*-(α-carboxy-2-nitrobenzyl)-L-glutamic acid; L-glutamic acid, α-(4,5-dimethoxy-2-nitrobenzyl) ester; and L-glutamic acid, γ-(α-carboxy-2-nitrobenzyl) ester; and biologically acceptable salts thereof. Each of the foregoing, representative, photoabsorbent molecules can be released from a neuroactive molecule using light having a wavelength of less than 360 nm. In general, the wavelength of light useful for releasing a photoabsorbent molecule from a neuroactive molecule is primarily determined by the chemical structure of the photoabsorbent molecule, and can be readily determined by one of ordinary skill in the art. The foregoing photoactivatable precursor molecules are commercially available from Molecular Probes, 4849 Pitchford Ave., Eugene, OR 97402-9165, U.S.A.

Some embodiments of the methods of the invention include the step of providing a photoactivatable precursor molecule to the mammalian retina before irradiating the

retina with light energy. A photoactivatable precursor molecule can be provided to the retina of a mammalian eye by any useful means. For example, photoactivatable precursor molecules can be injected into the eye, such as into the posterior chamber of the eye, or can be applied to the eye as a solution, gel, or ointment and absorbed across the cornea. For example, the photoactivatable precursor molecule can be chemically modified to enhance its hydrophobicity, thereby promoting its absorption into the retina. Again by way of example, the photoactivatable precursor molecule can be incorporated into a sustained release drug delivery device which is implanted into the eye, such as into the posterior chamber of the eye. The photoactivatable precursor molecule is released from the drug delivery device over time. Examples of useful sustained release drug delivery devices are set forth in the following United States patents, each of which is incorporated herein by reference in its entirety: United States Patent Numbers 5,902,598; 4,300,557; 5,378,475; 5,098,443; and 5,466,233.

Again by way of example, light-activated lipid vesicles, that contain photoactivatable precursor molecules, can be injected into the eyeball. Irradiation of the injected lipid vesicles with light energy releases the photoactivatable precursor molecules which penetrate, or otherwise physically associate with, the retina. A representative example of useful, light-activated, lipid vesicles are described in Gerasimov, O.V., et al., *Adv. Drug Delivery Reviews*, **38**:317-338, which publication is incorporated herein by reference.

Irradiation of the retina, to release neuroactive molecules from photoactivatable precursor molecules, can be achieved by any useful light source, such as a mercury arc lamp. Presently preferred light sources are lasers. Lasers can be tuned to a desired wavelength of light, and can deliver light to the retina at very high resolution and intensity. Typically, the laser is tuned to deliver light at a frequency that is optimal for releasing a neuroactive molecule from a photoactivatable precursor molecule. In some embodiments of the invention, the lens of one or both eyes of a mammalian subject is/are removed and replaced with an artificial lens that is better adapted to focus light energy onto the retina.

In some embodiments of the present invention, electrical signals (that encode information that represents a visual image) are provided to a laser, and directs the laser to scan a beam of light across the retina, thereby forming a pattern of light intensities on the retina. The laser light stimulates the release of neuroactive molecules from

photoactivatable precursor molecules disposed upon, and/or within, the retina. The amount of neuroactive molecules released at a given location on the retina is proportional to the amount of laser light that illuminates that location (*i.e.*, higher light intensity releases more neuroactive molecules than lower light intensity). The released neuroactive molecules interact with neurons within the retina and stimulate nerve impulses. Thus, the pattern of light intensities generates a corresponding pattern of nerve impulses within the retina that are communicated to the brain, which uses this information to construct a mental picture of the visual image (*i.e.*, the brain "sees" the visual image). Preferably the laser generates a beam of light of sufficiently high resolution to generate a visual image that approximates, or equals, the resolution of normal sight.

Thus, in some embodiments, the present invention provides methods for modulating neural activity in the retina of a mammalian eye, wherein the methods comprise the step of providing an electrical signal to a laser, wherein the electrical signal directs the laser to scan a beam of light energy across a retina, that includes one or more photoactivatable precursor molecules, thereby forming a pattern of light intensities on the retina, and wherein the pattern of light intensities releases one or more neuroactive molecules from the one or more photoactivatable precursor molecules, thereby generating a pattern of nerve impulses within the retina that are communicated to the brain and that provide visual information to the brain.

The electrical signal can be provided to the laser, for example, by a camera that forms a static or moving visual image of an object and/or a scene. Again by way of example, the electrical signal can be provided to the laser by a computer. The laser, computer and camera may, or may not, be portable by the mammalian subject to be treated in accordance with the methods of the present invention. Representative examples of apparatuses that can be used in the practice of the present invention to scan a beam of light energy across a mammalian retina, and thereby modulate neural activity in the retina, are set forth in the following United States Patents: United States Patent Numbers 5,355,181; 5,467,104; 5,596,339; 5,727,098; and 6,046,720, which patents are incorporated herein by reference in their entirety.

The FIGURE shows a representative embodiment of a system 10 for practicing a method of the invention. System 10 includes a wearable headpiece 12, a laser 14, an electronic shutter and modulator 16, a group velocity dispersion compensator 18, a scan controller 20, a lens 22, and a computer 24. In operation, light emitted from laser 14

passes through electronic shutter and modulator 16, and group velocity dispersion compensator 18 (which pre-chips the light pulses), and is focussed by lens 22, and thereafter is conducted through a fiber optic cable 26 that is connected to wearable headpiece 12. Light emerging from fiber optic cable 26 is focussed onto, and scanned across, the retina of the wearer of wearable headpiece 12. For example, light emerging from fiber optic cable 26 can be directed onto a mirror, or beam splitter, and thereafter directed through an ocular lens that focusses the light onto the retina of the wearer of wearable headpiece 12.

Electronic shutter and modulator 16 is controlled by electrical signals from computer 24 and serves to interrupt the beam of light energy produced by laser 14, thereby producing light and dark areas on the retina of the wearer of wearable headpiece 12 when the beam of light energy is scanned across the retina. Electronic shutter and modulator 16 also controls the intensity of the beam of light energy produced by laser 14.

Computer 24 also generates electrical signals that control scan controller 20 which controls a scanner (not shown) located in, or closely associated with, wearable headpiece 12, thereby controlling the path, across the retina, of the beam of laser light emitted from fiber-optic cable 26. For example, the scanner can incorporate one or more piezoelectric elements that vibratably control the motion of the tip of fiber-optic cable 26 located within wearable headpiece 12, thereby scanning light, horizontally and/or vertically, across the retina of the wearer of wearable headpiece 12.

Laser 14 can include more than one operably linked lasers; for example, laser 14 can include a green pump laser operably linked to a Ti:sapphire laser. Exemplary performance characteristics of laser 14 are a 100 fs pulse train at 82 MHz repetition at 690-050 nm (tunable).

The following examples merely illustrate the best mode now contemplated for practicing the invention, but should not be construed to limit the invention.

EXAMPLE 1

This Example shows the use of ultraviolet light energy to cleave a photoabsorbent molecule (DNMB) from a fluorescent molecule (FITC) in a rat retina *in vitro*.

Sprague-Dawley rats were kept for five days in constant illumination to eliminate all photoreceptors. Some animals from the same group were sacrificed and their retinas processed for histological analysis to verify that all photoreceptors were indeed

eliminated by this treatment. One animal from this group was sacrificed according to procedures approved by the Animal Care Committee at the University of Washington. One eye was then removed and dissected to separate the retina from the scleral tissue and pigmented epithelia.

The isolated retina was first incubated in a solution of DNMB-FITC dextran (Molecular Probes, 4849 Pitchford Ave., Eugene, OR 97402-9165) for ten minutes and then flattened onto a microscope slide and viewed with an Epi-fluorescent-equipped microscope (Zeiss). The retina was first viewed with FITC filters to verify that there was no obvious fluorescent signal in the retina. The retina was then exposed to a small spot (250 μm) of a shuttered mercury arc source (100 Watt) for two seconds through an ultraviolet filter. The retina was then viewed again through FITC filters, and a clear spot of fluorescence was now observed. Thus, the DMNB-FITC (which is not fluorescent) was cleaved by the light energy from the mercury arc source to release FITC, which appeared as a fluorescent spot when viewed through FITC filters. The FITC was released in a region that was approximately the same size as the illuminated spot on the retina, and there was little diffusion from the area of illumination.

Example 2

This Example shows the use of ultraviolet light energy to cleave a photoabsorbent molecule (DNMB) from a fluorescent molecule (FITC) in a rat retina *in vivo*.

Sprague-Dawley rats were kept for five days in constant illumination to eliminate all photoreceptors. Some animals from the same group were sacrificed and their retinas processed for histological analysis to verify that all photoreceptors were indeed eliminated by this treatment.

One animal from this group was anaesthetized according to procedures approved by the Animal Care Committee at the University of Washington. The animal received an intra-ocular injection of DMNB-FITC in one eye. A shuttered mercury arc source was focussed, via fused silica fiber optics, directly onto the retina through a 25x Zeiss Neo-fluar objective. After a two-second exposure, the animal was sacrificed by overanaesthesia, the eye was removed and dissected to separate the retina from scleral tissue and pigmented epithelia. The isolated retina was then flattened onto a microscope slide and viewed with an Epi-fluorescent-equipped microscope (Zeiss).

A small spot of fluorescent FITC was observed that was smaller in size than the spot that was observed in the *in vitro* experiment reported in Example 1 herein. The

smaller size of the spot of released FITC was likely due to the fact that the optics focussed the output from the fiber optics to a smaller diameter in the experiment reported in this Example, compared to the experiment reported in Example 1.

Example 3

This Example shows the use of ultraviolet light energy to cleave a photoabsorbent molecule (CNB) from a neuroactive molecule (glutamate) in a rat retina *in vivo*, thereby stimulating electrical activity in the superior colliculus, which is a portion of the rat brain that processes visual information.

Long-Evans rats were used in this experiment. These animals were normal and had normal vision. One animal was anaesthetized according to procedures approved by the Animal Care Committee at the University of Washington. The superior colliculus of the anaesthetized rat was exposed by a surgical crainiotomy, and a recording electrode was placed into the anterior lateral surface of the superior colliculus. Both light-ON and light-OFF visual responses could be elicited. After a series of normal light responses were recorded, all ON responses were blocked with an intraocular injection of aminophosphobutyric acid (APB). After twenty minutes, when no activity could be elicited to light-ON, the eye was then injected with CNB-glutamate. The retina was then illuminated with the shuttered mercury arc source. Responses to light-ON were elicited again, although these were variable and of longer duration than normal light-ON responses.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for modulating neural activity in the retina of a mammalian eye, said method comprising the step of irradiating the retina of a mammalian eye with light energy, wherein:

(a) the retina comprises a photoactivatable precursor molecule comprising a neuroactive molecule linked to a photoabsorbent molecule; and

(b) the light energy releases the neuroactive molecule from the photoabsorbent molecule, said released neuroactive molecule interacting with one or more retinal neurons thereby modulating neural activity in the retina.

2. The method of Claim 1 wherein the neuroactive molecule is selected from the group consisting of Ca^{2+}, glutamate, glycine, γ-aminobutyric acid, acetylcholine, dopamine, substance-P, and γ-guanosine triphosphate.

3. The method of Claim 1 wherein the neuroactive molecule is glutamate.

4. The method of Claim 1 wherein the photoabsorbent molecule is selected from the group consisting of a nitrobenzyl group, a trans-*o*-cinnamoyl group and an *m*-nitrophenyl group.

5. The method of Claim 4 wherein the photoabsorbent molecule is a nitrobenzyl group selected from the group of nitrobenzyl groups consisting of carboxy-2-nitrobenzyl, 4,5-dimethoxy-2-nitrobenzyl, and 5-carboxymethoxy-2-nitrobenzyl.

6. The method of Claim 1 wherein the photoabsorbent molecule is selected from the group consisting of a nitrobenzyl group, a trans-*o*-cinnamoyl group and an *m*-nitrophenyl group, and the neuroactive molecule is selected from the group consisting of Ca^{2+}, glutamate, glycine, γ-aminobutyric acid, acetylcholine, dopamine, substance-P, and γ-guanosine triphosphate.

7. The method of Claim 1 wherein the photoactivatable precursor molecule is selected from the group consisting of *N*-(α-carboxy-2-nitrobenzyl)carbamylcholine; γ–aminobutyric acid α-carboxy-2-nitrobenzyl ester; *N*-methyl-D-aspartic acid,

β-(2,2'-dinitrobenzhydryl) ester; *N*-(α-carboxy-2-nitrobenzyl)-L-glutamic acid; L-glutamic acid, α-(4,5-dimethoxy-2-nitrobenzyl) ester; L-glutamic acid γ-(α-carboxy-2-nitrobenzyl) ester; and biologically acceptable salts thereof.

8. The method of Claim 1 further comprising the step of providing the photoactivatable precursor molecule to the retina before irradiating the retina with light energy.

9. The method of Claim 8 wherein the photoactivatable precursor molecule is injected into the mammalian eye.

10. The method of Claim 8 wherein the photoactivatable precursor molecule is absorbed across the cornea of the eye.

11. The method of Claim 8 wherein the photoactivatable precursor molecule is released from a sustained release drug delivery device that is implanted into the eye.

12. The method of Claim 1 wherein a laser is utilized to irradiate the retina.

13. The method of Claim 1 wherein the modulated neural activity in the retina is communicated to the brain to yield visual information.

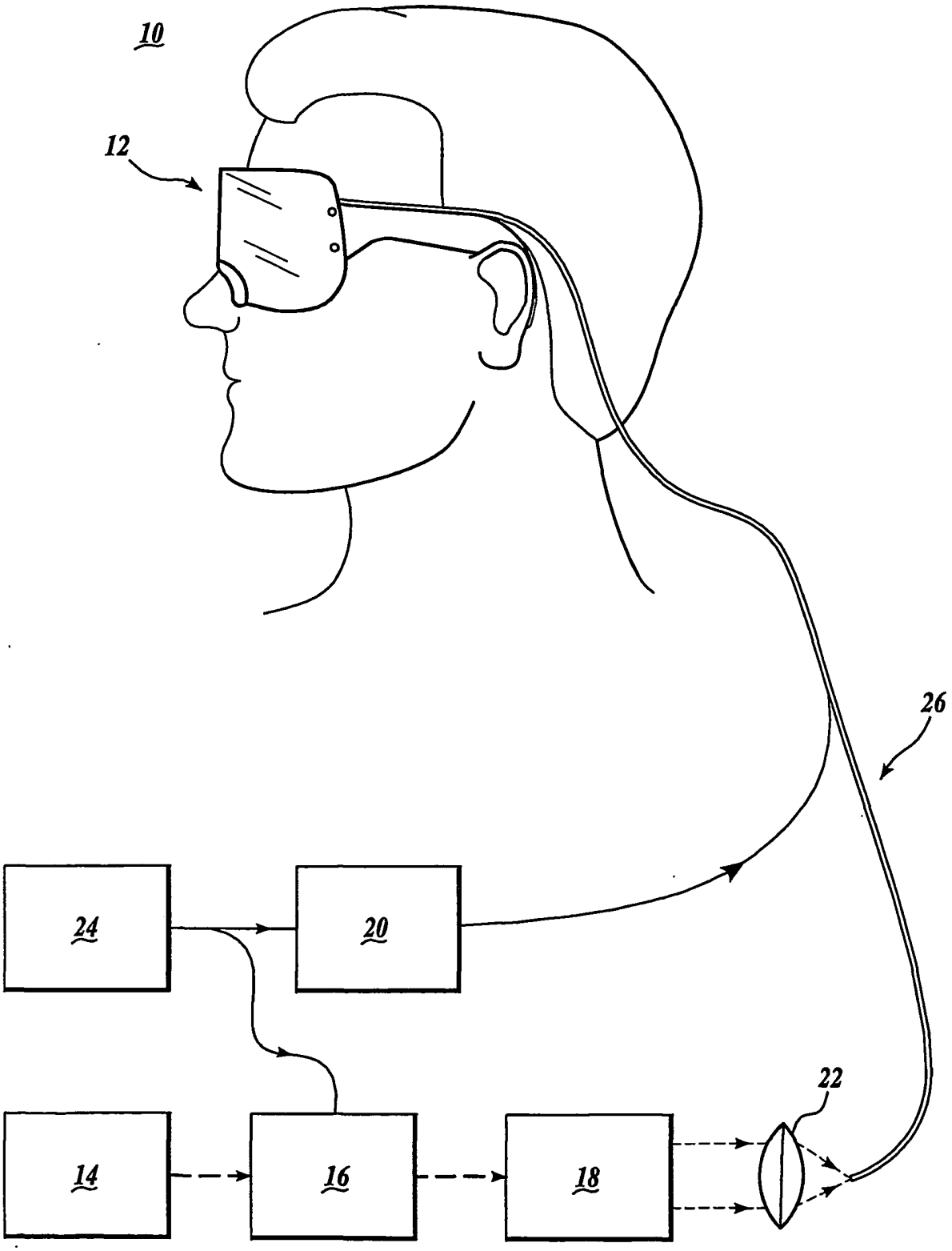
14. The method of Claim 12 wherein the laser is directed by an electrical signal from an optical device to scan light energy across the retina.

15. The method of Claim 12 wherein the laser is directed by an electrical signal from a computer to scan light energy across the retina.

16. A method for modulating neural activity in the retina of a mammalian eye, wherein said method comprises the step of providing an electrical signal to a laser, said electrical signal directing the laser to scan a beam of light energy across a mammalian retina, thereby forming a pattern of light intensities on the retina, wherein:

(a) the retina comprises one or more photoactivatable precursor molecules that each comprise a neuroactive molecule linked to a photoabsorbent molecule; and

(b) the pattern of light intensities releases one or more neuroactive molecules from the one or more photoactivatable precursor molecules, thereby generating a pattern of nerve impulses within the retina that are communicated to the brain and that provide visual information to the brain.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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/09342

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61B 18/18
US CL : 604/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 604/2, 3, 4, 10-14; 604/20, 21; 128/898

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,534,615 A (BAKER et al.) 09 July 1996 (09.07.1996), see entire document.	1-3, 16
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Y		4-15
Y	US 5,792,743 A (SCHACHNER) 11 August 1998 (11.08.1998), see entire document.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2002 (14.07.2002)	19 AUG 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer David Shay Telephone No. (703) 308-2215

Form PCT/ISA/210 (second sheet) (July 1998)